REMARKS

Original claims 41, 44, 49-52, 54-57, 59-60, 62, 64-66, and 71 and new claim 114 are currently pending in this application. Applicants have canceled claims 1-40, 42, 43, 45-48, 53, 58, 61, 63, 67-70, and 72-113 without prejudice to the Applicants' right to file one or more continuation, divisional, or continuation-in-part applications. Claim 41 has been amended for clerical purposes and not for reasons related to patentability. Claim 60 has been amended to clarify the claim in that y is not 0, since as recited by the independent claim 41, as filed, if y is 0, then the A_c group of P_{Hc2} must be a terminating group. *See* Specification at page 5, lines 10-14. New claim 114 has been added to recite a water-soluble peptidic substrate having the formula consistent with that of the species election filed in the Response to the Restriction Requirement submitted on March 12, 2004, which the Examiner stated was not found in the prior art. *See* Office Action at page 4, No. 8. Support for this substrate can be found in the specification, as filed, at page 34, Scheme 2. No new matter has been introduced into this application.

In view of the amendments and the following remarks, Applicants respectfully request reconsideration and reexamination of this application and timely allowance of the pending claims.

I. The Rejections Under 35 U.S.C. § 102(b) Should Be Withdrawn

Claims 41, 49-52, 54-57, 59-60, and 71 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,853,723 to Jacobs *et al.* ("Jacobs").

Claims 41, 44, 49-52, 60, 64-66, and 71 were also rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,876,946 to Burbaum *et al.* ("Burbaum").

Applicants respectfully traverse each of these rejections for the reasons set forth herein.

Anticipation is established under 35 U.S.C. § 102(b) when a single prior art reference, published more than one year prior to the earliest applicable priority date of the subject patent, discloses, expressly or under principles of inherency, each and every element of a claimed invention. *EMI Group N. Am. v. Cypress Semiconductor*, 268 F.3d 1342, 1350 (Fed. Cir. 2001); *Telemac Cellular Corp. v. Topp Telecom Inc.*, 247 F.3d 1316, 1327 (Fed. Cir.

2001); *Mehl/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999); *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply*, 45 F.3d 1550, 1554 (Fed. Cir. 1995). It is settled law that a prior art reference must disclose all of the elements of a claim in order to anticipate the invention recited by that claim. *See Manual of Patent Examining Procedure* § 2131. There must be no difference between the claimed invention and the reference disclosure as viewed by one of ordinary skill in the art. *See Scripps Clinic & Research Fdn. v. Genentech*, 927 F.2d 1565, 1576 (Fed. Cir. 1991).

A. The Anticipation Rejection Over Jacobs Should Be Withdrawn

According to the Office Action, Jacobs discloses a library of peptidic substrates. The peptidic substrates comprise an antibody (peptide (Ps)) coupled to polyethylene glycol (PEG) that is labeled with fluorescein isothiocyanate (*F). The Examiner alleges that the peptidic substrate of Jacobs reads on the claimed substrate member with the general formula *F-R_1-L_1-R_2-P_{Hc1}-P_S-P_{Hc2}-(R_3-L_2-R_4-T)$_y$ wherein y is 0, both P_{HC1} and P_{HC2} are covalent bonds, L_1 is PEG, R_1 is a covalent bond consisting of a sulfur heteroatom and R_2 is a thioether covalent linkage. *See* Office Action at page 5. Applicants respectfully point out that each any every element of the claimed invention is not disclosed in Jacobs.

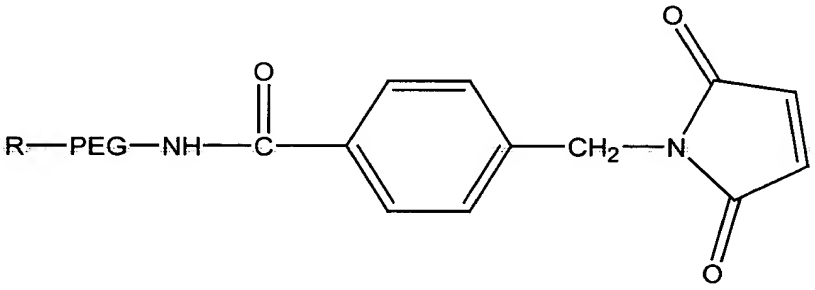
Jacobs discloses a composition comprising (a) an immunologically active monoclonal antibody or fragment thereof against glutamic acid decarboxylase coupled to (b) a nonimmunogenic hydrophilic polymer that provides a hydration shell around the monoclonal antibody or fragment thereof for inhibiting immune recognition. *See* Jacobs at col. 6, lines 5-10. According to the specification, the polymer is a poly(ethylene glycol), and in one illustrative preferred embodiment, the monoclonal antibody and polymer are covalently coupled together with a crosslinker. *Id.* at lines 11 and 20-22. Jacobs further discloses a monosubstituted sulfosuccinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC)-PEG-amine labeled with fluorescein isothiocyanate. *Id.* at col. 13, line 65 to col. 14, line 12.

The compositions disclosed in Jacobs fail to disclose each and every element of the recited claims. In particular, Jacobs does not disclose the groups P_{Hc2} and P_s of the water-soluble peptidic susbtrate recited by the pending claims.

According to the Office Action, P_{Hc1} and P_{Hc2} are each a covalent bond. *See* Office Action at page 5. Specifically, the Examiner alleged on page 5 of the Office Action, "the peptidic substrates of Jacobs *et al.* read on the claimed substrate member with the general formula of *F-R_1-L_1-R_2-P_{Hc1}-P_S-P_{Hc2}-(R_3-L_2-R_4-T)$_y$ wherein y is 0 both P_{Hc1} and P_{Hc2} are covalent bond..." *Id.* However, closer inspection of the claims will reveal that P_{Hc1} and P_{Hc2} cannot each simultaneously be a covalent bond. In particular, if y = 0, P_{Hc1} can be a covalent bond but when y = 0, at the very least, P_{Hc2} must be a terminating group selected from the group consisting of alcohol moieties, amine moieties, ester moieties, ether moieties, carboxylic acid moieties, amide moieties, and sulfonic acid moieties. *See* Specification at page 48, lines 23 to page 49, line 13.

Applicants further submit that Jacobs is also silent with regard to P_s (*i.e.*, a peptide from 5 to 25 amino acids in length).

Jacobs discloses compounds of the following structure[1]:



wherein R is a label such as Bolton-Hunter reagent or fluorescein isothiocyanate. *See* Fig. 2 and col. 6, lines 47-50.

In contrast to the library consisting of a plurality of water-soluble peptidic substrates, wherein each peptidic substrate member of the library has the general formula:

*F-R_1-L_1-R_2-P_{Hc1}-P_S-P_{Hc2}-(R_3-L_2-R_4-T)$_y$

1 Applicants point out that the structures illustrated in Jacobs in Figure 2 is incorrect. The structure includes an additional oxygen atom between the amine group of the PEG and the carbonyl group on the benzene ring. The structure illustrated above in this amendment is the correct structure.

each and every element of the claimed invention is not disclosed in Jacobs. In particular, the following Table illustrates that in mapping the structure disclosed in Jacobs to the above peptidic substrate of the claimed invention, P_s and P_{Hc2} are each not disclosed in Jacobs.

Peptidic Substrate of the Claimed Invention	**Jacobs**
*F	R (label)
R_1	covalent bond
L_1	PEG
R_2	covalent bond
P_{Hc1}	covalent bond
P_s	absent
P_{Hc2}	absent

$Y = 0$ therefore $(R_3\text{-}L_2\text{-}R_4\text{-}T)_y$ is not present.

Applicants respectfully submit that because the legally required disclosure of each and every element of the claimed invention is not disclosed in Jacobs (*i.e.*, the groups P_{Hc2} and Ps are absent from Jacobs), the rejection of claims 41, 49-52, 54-57, 59-60, and 71 under 35 U.S.C. § 102(b) should be withdrawn.

B. The Anticipation Rejection Under Burbaum Should Be Withdrawn

According to the Office Action, Burbaum discloses a library of peptidic substrates, wherein the peptidic substrate comprises a peptide (Ps) with a kinase domain affixed to a polymer bead and labeled with Cy5 (*F). *See* Office Action at page 6. The peptide comprises "end" residues (P_{Hc1} and P_{Hc2}) with different net charges. *Id.* The polymer bead includes PEG-grafted polystyrene bead. *Id.* The label includes fluorescent labels such as Texas red and chemiluminescent labels. *Id.* The Office Action alleges that the peptidic substrates of Burbaum read on the claimed substrate member with the general formula of *F-R_1-L_1-R_2-P_{Hc1}-P_S-P_{Hc2}-$(R_3\text{-}L_2\text{-}R_4\text{-}T)_y$ wherein y is 0, L_1 is PEG, R_1 is a covalent bond consisting of a nitrogen heteroatom and R_2 is a covalent bond consisting of an oxygen heteroatom. *Id.* Applicants respectfully traverse this rejection for the reasons set forth herein.

Burbaum is directed to a high throughput assay for rapidly screening a plurality of compounds. *See* Burbaum at col. 2, lines 55-56. The assay determines the degree of inhibition by the compounds of a ligand/receptor interaction, or of an enzyme catalyzed reaction, or the degree of binding of library compounds to a target molecule. *Id.* at lines 56-60. Inhibition (or binding) by the library compounds causes a change in the amount of an optically detectable label that is bound either to suspendable cells or to suspendable solid supports. *Id* at lines 60-63. These amounts are compared with the amount of label that is not bound to individual cells or solid supports (*i.e.*, background signal). *Id.* at col. 2, line 66 to col. 3, line 1.

Applicants respectfully submit that the claimed invention is directed to a library consisting of a plurality of water-soluble peptidic susbtrates. *See, for example*, claim 41 at Specification, page 48, line 4 to page 49, line 22. In contrast, the assay of Burbaum utilizes binding of a label to suspendable cells or to suspendable solid supports, which are by definition insoluble. In particular, Burbaum discloses that the suspended cells (or suspended solid supports) are allowed to settle for about 10 minutes or more, so that more than about 75% of the cells or supports are contained in less than about 25% of the volume of the assay container, (*i.e.*, a cell or solid support layer forms on the bottom). *See* Burbaum at col. 5, lines 53-58. Most preferably, more than 90% of the cells or supports are allowed to settle in less than about 10% of the volume of the container. *Id.* at lines 58-60. Moreover, Burbaum further discloses:

> Suspendable solid support is intended to refer to any solid support capable of being suspended in a liquid. The support should be small enough so it does not block optical access to the rest of the solution upon settling to the bottom of the assay well. On the other hand, the support should be large enough so that it does not remain in suspension for an extended period of time after the assay components are combined. The preferred supports are less than about 50 μm in diameter, most preferably less than 10 μm in diameter.

Id. at col. 6, lines 28-36.

For these reasons, Applicants respectfully submit that because Burbaum is directed to affixing compounds to a solid support or polymer bead (each of which is insoluble), in contrast to the water-soluble peptidic substrate of the claimed invention, the rejection of claims 41, 44, 49-52, 60, 64-66, and 71 under § 102(b) should be withdrawn.

II. The Rejection Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 41, 44, 49-52, 54-57, 59-60, 62, 64-66, and 71 were rejected on pages 7-9 of the Office Action under 35 U.S.C. § 103(a) as allegedly obvious over Jacobs and Pomroy *et al., Biochemical and Biophysical Research Communications*, **1998**, 245(2), 618-621 ("Pomroy").

Claims 41, 49-52, 54-57, 59-60, 62, 64-66, and 71 were rejected on pages 9-10 of the Office Action under 35 U.S.C. § 103(a) as allegedly obvious over Lam *et al,. Int. J. Peptide Protein Res.*, **1995**, 45(6): 587-592 and Jacobs.

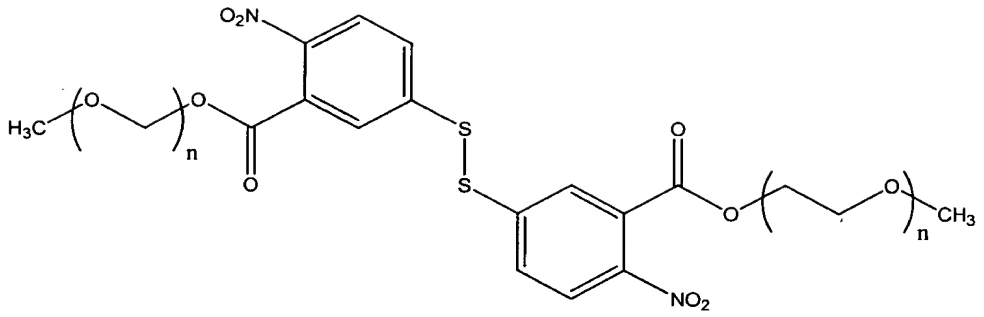
The Federal Circuit has set forth three basic criteria that must be met to establish a case of *prima facia* obviousness. First, there must have been at the time of the invention a motivation to combine or modify the teachings of the references cited. *Ecolochem, Inc. v. Southern California Edison Company*, 227 F.3d 1361, 1372 (Fed. Cir. 2000) (holding obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination); *see also In re Jones*, 958 F.2d 347 (Fed. Cir. 1992); *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988) (holding that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art). Second, the alleged prior art must teach or suggest all of the limitations of the claims alleged to be obvious. *In re Royka*, 490 F.2d 488 (CCPA 1974) (holding that to establish *prima facia* obviousness of a claimed invention, all of the claim limitations must be taught or suggested by the prior art); *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991) (holding that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure). Third, there must have been at the time of the invention a reasonable expectation of success. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1207-1208 (Fed. Cir. 1991), *cert. denied* 502 U.S. 856 (1991) (holding that obviousness requires references to show that there was, at the time of the invention, a reasonable expectation of success).

A. The Rejections Over Jacobs In View Of Pomroy Under 35 U.S.C. § 103(a) Should be Withdrawn

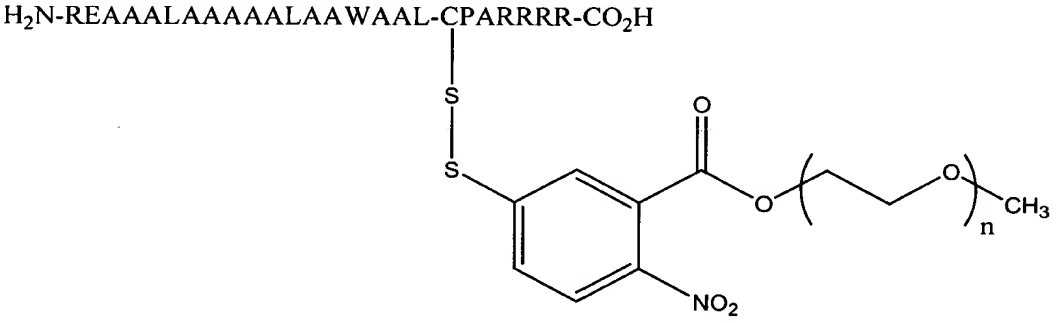
According to the Office Action, it is alleged that it would have been obvious to one of ordinary skill in the art at the time the invention was made to include coupling the peptide to the PEG by way of the cysteine of the peptidic portion and the "end" residues of the peptide having a different net charged as taught by Pomroy. *See* Office Action at pages 8. Particularly, the Office Action alleges that one of ordinary skill in the art would have been motivated to include coupling the peptide to the PEG by way of the cysteine of the peptidic portion and the end residues (*i.e.*, P_{Hc1} and P_{Hc2}) of the peptide having a different net charged in the library of Jacobs for the advantage of providing a PEG reagent that can perform under mild reaction conditions allowing for the PEGylation of a target protein under non-denaturing conditions since both Jacobs and Pomroy disclose compositions, wherein the peptide is coupled to the PEG. *Id.* Furthermore, it is alleged that one of ordinary skill in the art would have a reasonable expectation of success in the combination of Jacobs and Pomroy because Pomroy discloses the success of PEGylation of the peptide using PEG-a-Cys reagent. *Id.* at pages 8-9. Applicants respectfully traverse this rejection for the reasons set forth herein.

Applicants respectfully submit that the combination of Jacobs and Pomroy fails to teach or suggest the claimed invention. As stated above, Jacobs discloses a composition comprising (a) an immunologically active monoclonal antibody or fragment thereof against glutamic acid decarboxylase coupled to (b) a nonimmunogenic hydrophilic polymer that provides a hydration shell around the monoclonal antibody or fragment thereof for inhibiting immune recognition thereof. However, the compositions disclosed in Jacobs do not comprise the groups P_{Hc2} and P_s of the library consisting of water-soluble peptidic susbtrates recited by the pending claims. Pomroy fails to remedy the deficiencies of Jacobs.

Pomroy discloses a reagent useful for PEGylation of hydrophobic peptides. In particular, the PEGylation reagent has the following structure:



The reagent can react with hydrophobic peptides (*e.g.*, H_2N-REAAALAAAAALAAWAAL-CPARRRR-CO_2H, wherein C is cysteine; *see* Pomroy at page 619, col. 2, ¶ 5) to form the following PEGylated peptide:



Thus, Pomroy is merely concerned with solubilizing hydrophobic peptides to isolate and characterize transmembrane domains of membrane proteins using a reagent that is easily removed. Pomroy does not disclose or suggest attaching a detectable moiety. In fact, the only similarity between the claimed invention and the disclosure in Pomroy is connecting a PEG group to a peptide, which would hardly motivate one of ordinary skill in the art to modify Jacobs to obtain the claimed invention.

Applicants respectfully submit that the disclosures of the cited references simply provide no teaching, no suggestion, and no motivation to one of ordinary skill in the art to modify the elements of the cited references to produce the Applicants' claimed invention.

The Examiner states on page 10 of the Office Action,

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to include coupling the peptide to the PEG by way of the cysteine of the peptidic portion and the "end" residues of the peptide having a different net charged in the library of Jacobs for the advantage of providing a PEG reagent that can perform under mild conditions allowing for the PEGylation of a target protein under non-denaturing conditions since both Jacobs and Pomroy disclose compositions, wherein the peptide is coupled to the polyethylene glycol.

See Office Action at page 8.

Applicants respectfully submit that the invention is directed to a library consisting of a plurality of water-soluble peptidic substrates, wherein one of the elements of the substrate is a PEG moiety. Neither Jacobs nor Pomroy is directed to a screening assay library, much less a library consisting of water-soluble peptidic substrates, wherein each peptidic substrate member of the library has the general formula:

$$*F\text{-}R_1\text{-}L_1\text{-}R_2\text{-}P_{Hc1}\text{-}P_S\text{-}P_{Hc2}\text{-}(R_3\text{-}L_2\text{-}R_4\text{-}T)_y.$$

As the Examiner is aware, it is the invention as a whole that must be considered in obviousness considerations not bits and pieces of various references. *Hartness International, Inc. v. Simplimatic Engineering Co.*, 819 F.2d 1100 (Fed. Cir. 1987). Neither Jacobs nor Pomroy alone or in combination disclose or suggest the claimed invention. In order to contrive a *prima facia* case of obviousness, the combination of Jacobs and Pomroy requires one of ordinary skill in the art to impermissibly "pick and choose" the various elements recited by the claims at random from the cited references, which is only possible when using the present claims as a blueprint (*i.e.*, using impermissible hindsight). Applicants respectfully submit that only with the aid of impermissible hindsight could the library consisting of water soluble peptidic substrates, wherein each peptidic substrate member of the library has the general formula:

$$*F\text{-}R_1\text{-}L_1\text{-}R_2\text{-}P_{Hc1}\text{-}P_S\text{-}P_{Hc2}\text{-}(R_3\text{-}L_2\text{-}R_4\text{-}T)_y.$$

And, as the Examiner is aware, it is improper to use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. *In re Fine*, 837 F.2d 1071 Fed. Cir. 1988).

For these reasons, Applicants respectfully submit that the invention as recited by the pending claims is not obvious over Jacobs and Pomroy. Applicants further submit that because the combination of references fail to suggest the claimed invention, the rejection of claims 41, 44, 49-52, 54-57, 59-60, 62, 64-66, and 71 under § 103(a) should be withdrawn.

B. The Rejections Over Lam and Jacobs Under 35 U.S.C. § 103(a) Should be Withdrawn

According to the Office Action, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to include optically labeling the library as taught by Jacobs in the library of Lam. *See* Office Action at page 10. It is alleged that one of ordinary skill in the art would have been motivated to include optically labeling the library or Lam because the type of label used would be a choice of experimental design and is considered within the purview of the cited prior art. *Id.* It is further alleged that both Lam and Jacobs disclose the library of peptidic substrates comprise a peptide affixed to a polymer, wherein the polymer includes PEG and that one of ordinary skill in the art would have reasonable expectation of success in the combination of Lam and Jacobs because Jacobs discloses that the peptidic substates can be labeled with either a radioactive label or fluorescent label. *Id.* Thus according to the Office Action, the type of label use would be considered a choice of experimental design. Applicants respectfully traverse this rejection for the reasons set forth herein.

Applicants respectfully submit that the combination of Jacobs and Lam fails to teach or suggest the claimed invention. As stated above, Jacobs discloses a composition comprising (a) an immunologically active monoclonal antibody or fragment thereof against glutamic acid decarboxylase coupled to (b) a nonimmunogenic hydrophilic polymer that provides a hydration shell around the monoclonal antibody or fragment thereof for inhibiting immune recognition thereof. However, the compositions disclosed in Jacobs fail to disclose the groups P_{Hc2} and P_s of the water-soluble peptidic susbtrate recited by the pending claims, and Lam does not rectify the deficiencies of Jacobs.

Lam discloses a random peptide library affixed to a PEG-grafted polystyrene bead, with any given bead containing a single peptide entity. The peptide beads are treated with a protein kinase and gamma ^{32}P-ATP and then washed. The washed beads are mixed with hot

agarose and spread out on a glass plate. After the gel solidifies it is exposed to X-ray film. The radioactive beads are identified, collected, and submitted to protein sequencing.

In contrast, to the claimed library consisting of water soluble peptidic substrates, Lam utilizes a polystyrene bead, which is by definition insoluble. Thus, Lam actually teaches away from the claimed invention. Moreover, one of ordinary skill in the art after reading Lam would clearly not be motivated to combine or modify its teachings with the teachings of Jacobs to obtain the claimed invention, since the very disclosure of Lam is concerned with an insoluble system.

Applicants respectfully submit that the Examiner has failed to establish the legally required *prima facie* case of obviousness based on the disclosures of Jacobs and Lam. One of ordinary skill in the art would have had not motivation to combine the teachings of Lam, which is directed to an insoluble system with the disclosure of Jacobs. Even assuming *arguendo* one of ordinary skill in the art were motivated to make this leap to combine the references, the reference nonetheless fail to recite the claimed invention. In particular, both references fail to disclose the element P_{Hc2}, thus there is nothing in either disclosure that would motivate one of ordinary skill in the art to include this absent element to obtain the claimed invention.

To summarize, the combination of references fails to suggest the claimed invention and fails to motivate one of ordinary skill in the art to modify the teachings of the references to produce the claimed invention. The cited references alone or in combination fail to provide the legally required suggestion of the claimed library consisting of water-soluble peptidic substrates of general formula:

$$*F\text{-}R_1\text{-}L_1\text{-}R_2\text{-}P_{Hc1}\text{-}P_S\text{-}P_{Hc2}\text{-}(R_3\text{-}L_2\text{-}R_4\text{-}T)_y.$$

For these reasons, Applicants respectfully submit that the invention as recited by the pending claims is not obvious over Lam and Jacobs. Applicants further submit that because the combination of references fail to suggest the claimed invention, the rejection of claims 41, 44, 49-52, 54-57, 59-60, 62, 64-66, and 71 under § 103(a) should be withdrawn.

III. Conclusion

Respectfully, Applicants submit that the rejections to the claims in the application should be withdrawn based on the arguments made herein. Favorable consideration and a Notice of Allowance are earnestly solicited.

Except for issues payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310.

Dated: November 4, 2004

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